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Entropy production as a physical pacemaker of lifespan in mole-rats

L. Triana[1], G. Cocho[2], R. Mansilla[3], & J.M. Nieto-Villar[4*]

[1]Complete Pharmaceutics, Florida, United States of America.
[2]Instituto de Física de la UNAM, México
[3]Centro de Investigaciones Interdisciplinarias en Ciencias y Humanidades, UNAM, México.
[4]Department of Chemical-Physics, A. Alzola Group of Thermodynamics of Complex Systems of M.V. Lomonosov Chemistry Chair, Faculty of Chemistry, University of Havana, Cuba.

ABSTRACT

This work discusses the relationship of the biological aging between mole-rats and rats through a unified approach from the perspective of thermodynamics. Taking calorimetric data from some published studies of the metabolism on mole-rats and rats, it is calculated the entropy production rate. It is observed that the entropy production rate in rats decays with chronological age, and develops a kind of first order phase transition. However, the mole-rats, showed that entropy production rate did not change significantly with age and exhibits a slightly higher value as an average compared to the rats analyzed. This result can be interpreted in terms of a mole-rats exhibit a more robustness, i.e. greater plasticity than rats. Furthermore, it is shown that the entropy production rate could be consider as a physical marker of biological age and a predictor of Lifespan.

Keywords:
Aging, Longevity, Mole-rats, Metabolic rate, Biological phase transition, Entropy production rate

***Correspondence to Author:**
J.M. Nieto-Villar
Department of Chemical-Physics, A. Alzola Group of Thermodynamics of Complex Systems of M.V. Lomonosov Chemistry Chair, Faculty of Chemistry, University of Havana, Cuba.

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1. Introduction

Longevity and aging constitute one of the most important current challenges of the biomedical sciences. Regardless of all the achievements in molecular biology and genomics [1,2,3], so far, the underlying mechanisms of senescence remain largely a mystery and has puzzled the scientific community for a long time.

Traditionally for years rats and mice [4] have served as biological models for the study of aging and its manifestation through degenerative diseases, even though more than 50% of these die of cancer in old age [5].

Within the family of rodents has appeared a paradigmatic species, the mole-rats, which exhibit a longevity that considerably exceeds that of any other rodent and are resistant to the so-called degenerative diseases in particular cancer [6]. As a fact, the journal Science named the naked mole-rat "Vertebrate of the Year" for 2013 [7].

It is well known that metabolic processes are closely linked with aging, the action of reactive oxygen species ROS and the so-called degenerative diseases [8,9,10]. According to the theory given by Sohal [11,12], the rate of aging and metabolic rate of organisms are inversely correlated. Effects of metabolic rate on aging may be mediated by ROS. Antioxidant defenses tend to decline during aging, whereas the ROS induced damage appears to increase with age [13].

The pioneering work of McNab [14], directed basically the relationship between the level of metabolism and the characteristics of the fossorial environment rodents, he provide interesting data in relation to the metabolism of these animals wish live in closed burrows, where one can clearly define their microclimates.

To date, numerous studies have been focused on determining the metabolic rate for a mole-rats [15,16,17], finding as a general characteristic, that the mole-rat has an extremely low basal metabolic rate, can tolerate high levels of oxidative stress and have mechanisms to prevent age-related diseases, such as cancer, diabetes, and cardiovascular, brain, and liver diseases, as well as many infections [5,6].

The development of the thermodynamics of irreversible processes [18], complex systems theory [19] and systems biology [20] made possible to widen the scope of the study of biological systems. For example, those observations that show an age-related loss of complex variability in multiple physiologic processes including cardiovascular control, pulsatile hormone release, and electroencephalographic potentials [21,22,23].

A thermodynamics viewpoint may be useful for theory testing, since the adequacy of a postulated mechanism of aging is best judged by its compatibility with senescent changes [24]. In a previous study [25] we described the relationship between aging and cancer for healthy humans and patients with metastatic carcinoma in a unified approach from the perspective of thermodynamics. However, to our best knowledge, there are not reports related to thermodynamics analysis of the longevity of the mole-rats.

The main purpose of the present work is to extend the thermodynamics formalism previously developed [25] to discuss the relationship of the longevity between the mole-rats and rats. The manuscript is organized as follow: In Section 2 is presented a theoretical framework based on thermodynamic formalism, particularly the entropy production rate due to metabolic rate. In section 3, relationship between the entropy production rate and metabolic rate for mole-rats and rats is presented. Finally, some concluding remarks are presented.

2. Thermodynamics framework

As we know from classic thermodynamics, if the constraints of a system are the temperature T and the pressure P, then the entropy production can be evaluated using Gibbs's free energy [26], as:

$$\delta S_i = -\frac{1}{T} dG_{Tp} \quad (1)$$

If the time derivative of (1) is taken, we have:

$$\frac{\delta S_i}{dt} = -\frac{1}{T}\frac{dG_{Tp}}{dt} \quad (2)$$

where $\frac{\delta S_i}{dt}$ represents the entropy production rate, $\dot{S}_i$. The term $\frac{dG_{Tp}}{dt}$ can be developed by means of the chain rule as a function of the degree of advance of the reaction ξ as:

$$\frac{dG_{Tp}}{dt} = \left(\frac{\partial G}{\partial \xi}\right)_{Tp} \frac{d\xi}{dt} \quad (3)$$

where $\left(\frac{\partial G}{\partial \xi}\right)_{Tp}$, according to De Donder and Van Rysselberghe [27], represents the affinity $\mathrm{A} = -\left(\frac{\partial G}{\partial \xi}\right)_{Tp}$, and the term $\frac{d\xi}{dt}$ is the reaction rate $\dot{\xi}$. Using the expression for the Gibbs free energy, $G = H - TS$, we obtain

$$\mathrm{A} = -\left(\frac{\partial H}{\partial \xi}\right)_{Tp} + T\left(\frac{\partial S}{\partial \xi}\right)_{Tp} \quad (4)$$

The term $\left(\frac{\partial H}{\partial \xi}\right)_{Tp}$ represent the heat of process, r_{Tp}. Sometimes it is possible to neglect the term $\left(\frac{\partial S}{\partial \xi}\right)_{Tp}$, due to $\left|r_{Tp}\right| >> \left(\frac{\partial S}{\partial \xi}\right)_{Tp}$ [28]. Considering (3) and (4), we get that the entropy production rate can be rewritten as:

$$\frac{dS_i}{dt} \equiv \dot{S}_i = \frac{1}{T}\mathrm{A}\dot{\xi} \approx \frac{r_{Tp}\dot{\xi}}{T} = \frac{1}{T}\left(\frac{\delta q}{dt}\right)_{Tp} \quad (5)$$

where $\left(\frac{\delta q}{dt}\right)_{Tp} \equiv \dot{q}$, are the metabolic rate of oxygen consumption. The formula (5) is an approximation to determine the entropy production rate of a living organism [28]. The equation (5) can be rewritten according to Zotin [29] using the metabolic rate as follows:

$$\dot{S}_i = \frac{\dot{q}}{T_b} \quad (6)$$

where T_b is a body temperature in thermoneutral zones. To calculate the metabolic rate oxygen consumption was used, $\dot{V}O_2 \left[mL/g.h \right]$. The conversion of oxygen consumption to calories was based on the respiratory quotient *RQ* = 0.82, which corresponds to 4.8 kcal per 1 L of oxygen.

3. The entropy production rate for the rats and mole-rats

Thermodynamic framework of the aging process for the biologic systems permits us to see this problem as a whole, taking into account that the "whole" is more than the sum of its parts.

The rate of entropy production $\dot{S}_i$ can be determined from the formula (6) from oxygen consumption $\dot{V}O_2$ for albino rats from birth to the age of 4 months [30]. In Figure 1 is shown the rate of entropy production per body mass $\dot{S}_i$ for the albino rats for both sex and different age.

For both sex it was obtained the polynomial regression:

$$\dot{S}_i = a + b\Omega + c\Omega^2 + d\Omega^3; \quad (7)$$

where Ω represent the chronological age, and the constants of Eq. (7) are: for male ($a = 0.070 \pm 0.006$, b = -0.0014 $\pm$ 0.0003, c = 1.2E-5 $\pm$ 4E-6, d = –3E-8 $\pm$ 1E-8; R-square = 0.98866, SD=9.06224E-4, P<0.0001); and for female ($a = 0.074 \pm 0.007$, b = -0.0015 $\pm$ 0.0004, c = 1.3E-5 $\pm$ 5E-6, d = –4E-8 $\pm$ 2E-8; R-square=0.98042, SD=0,00111, P<0.0001).

The polynomial regression, Eq. (7), reminds the van der Waals equation of state [31], which it is useful to describe the first order phase transitions.

As can be seen, the female rats exhibit greater complexity (> $\dot{S}_i$) than to the male's ones, which implies greater robustness [32,33,34]. The higher entropy production rate observed in females in comparison with males is not

surprising, since it confers some stability and also robustness during the active period, since the females must ensure reproduction in a short period of time [4].

In Figure 2 is shown the rate of entropy production per body mass $\dot{S}_i$ from oxygen consumption $\dot{V}O_2$ for African giant rat [35] for different age.

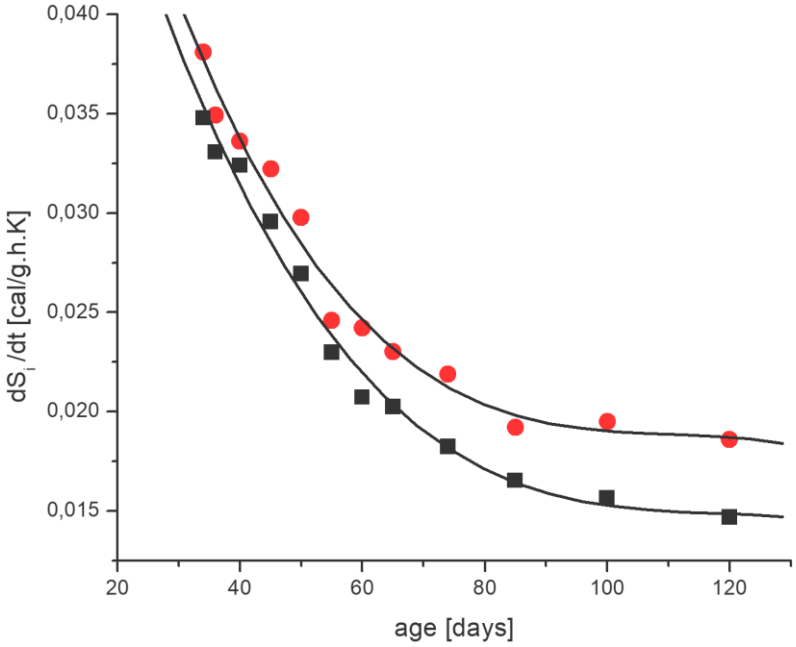

Fig. 1 The rate of entropy production per body mass $\dot{S}_i$ for the albino rats for both sex (black square points: male, circle red points-female) and different age. The body temperature $T_b = 308K$. Lifespan ~ 2.5-3.5 years

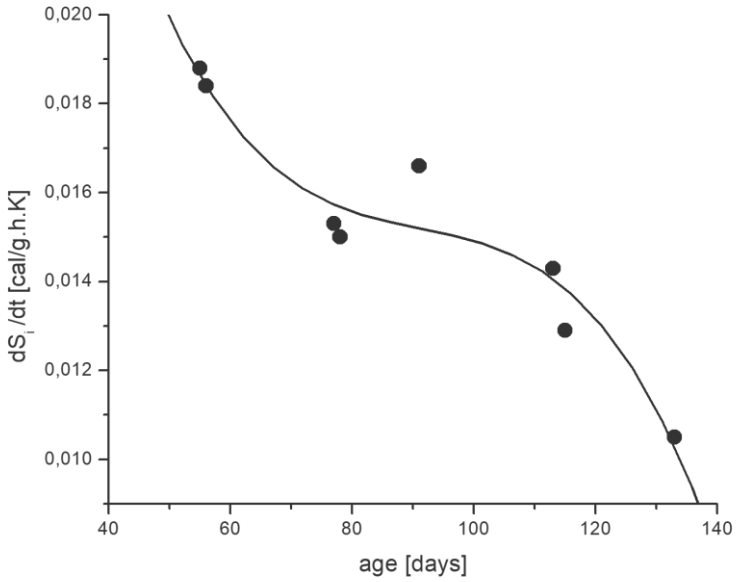

Fig. 2 The rate of entropy production per body mass $\dot{S}_i$ for the African giant rat and different age, the body temperature $T_b = 309.7K$. Lifespan ~ 7 years

It was obtained the polynomial regression:

$$\dot{S}_i = a + b\Omega + c\Omega^2 + d\Omega^3; \quad (8)$$

where Ω represent the chronological age, and the constants of Eq. (8) are: $a = 0.06 \pm 0.02$, $b = \text{-}0.0013 \pm 0.0006$, $c = 1\text{E-}5 \pm 7\text{E-}6$, $d = -5\text{E-}8 \pm 2\text{E-}8$; R-square=0.93202, SD=9.52572E-4, P<0.0001).

As can be seen, the polynomial regression, Eq. (8), like the one obtained for the albino rats Eq. (7), describes the aging process as the first order phase transitions. A similar result is found in a previous work for healthy humans and patients with metastatic carcinoma [25].

This evidence give us a plausible response to the emergence of aging processes, and allow us to postulate that they are activated through what it could be called “biological phase transition”.

Generally, it is seen that with increase of age, the entropy production rate decreases, i.e., decreases the complexity, as other authors have pointed out [36].

In a previous work [37] we have shown that the rate of entropy production is a Lyapunov function, in fact we extended this formalism to the development of cancer [38,39,40,41,42]. Thus, we have the entropy production per unit time meets the necessary and sufficient conditions for Lyapunov function [51], such that

$$\dot{S}_i = f(\Omega) > 0, \quad (9)$$

where Ω is the vector of control parameters. In this case, we take the age of the subjects as the control parameter $(\Omega \equiv \text{age})$. The Eulerian derivative (9) must hold:

$$\frac{d\dot{S}_i}{dt} = \frac{\partial \dot{S}_i}{\partial \Omega}\frac{d\Omega}{dt} \leq 0; \quad (10)$$

Since, as it is natural, Ω is related with chronological age, $\frac{d\Omega}{dt} > 0$, then it fulfills that: $\frac{\partial \dot{S}_i}{\partial \Omega} \leq 0$, which can be demonstrated from Eq. (7), (8) and also shown in Figure 1,2. That allows us to affirm that the entropy production rate is a Lyapunov function, i.e., shows the directional character of the aging process.

We arrive by this way that the activation of the aging processes occurs on a natural way in mammals. This conjecture is according to the theory given by Cutler [43,44] where each mammalian species is characterized by a lifespan. Physiological and psychological changes that occur by aging have shown to indicate the biological age of the individual [45].

As point out by Strehler [46], who defines aging by means of four postulates, we could add a fifth one: the aging processes are a complex network of interactions self-organized in time and space, far from thermodynamic equilibrium, exhibiting high complexity, robustness and adaptability, whose physiological functions decline with age [25].

As discussed in the introduction, mole-rats are a paradigmatic species, which exhibit a longevity that considerably exceeds that of any other rodent with a similar body mass and are resistant to so-called degenerative diseases, such as cancer [6]. Albeit that energy metabolism plays an important role in aging but, it is not clear how this happens.

Table 1 shows the rate of entropy production per body mass $\dot{S}_i$ for the mole-rats.

A general characteristic is observed, is that as an average the rate of entropy production per body mass $\dot{S}_i$ of the mole-rats is slightly higher compared to the rats (see Fig.1,2). The most significant is that according to O'Connor *et al.* [17,50], metabolic rate of the Naked mole-rat did not change significantly with age, which implies that unlike rats (see Fig. 1,2) and humans [25], the rate of entropy production per body mass is a constant during life, which gives it a high degree of robustness (plasticity) [32,33,34]. This result is consistent with the hypothesis that naked mole rats are characterized by neoteny with the preservation of the characteristics of adolescences [51] and could be explain the high resistance to the degenerative diseases of the moles rats.

Apparently given the living conditions of the mole-rats, they have managed to develop a metabolic advantage, which has been found in a series of studies in non-human primates and humans indicating that calorie restriction (CR) results in a decrease in metabolic rate that is greater than that expected on the basis of the loss of tissue mass; This phenomenon, referred to as “metabolic adaptation”, was associated with less oxidative damage to DNA [52].

Table 1 The rate of entropy production per body mass $\dot{S}_i$ for the mole-rats

mole-rats	T_b [*K*]	$\dot{V}O_2 \left[mL/g.h \right]$	$\dot{S}_i \left[cal/g.h.K \right]$	Lifespan [years]
Heterocephalus glaber [47] normoxic (21% O_2) hypoxia (7% O_2) [16]	304.5 302.2 305.4	1.674 0.624 0.97	0.0264 0.0097 0.0152	32
Fukomys anselli [48] reproductive animals non-reproductive	309.1	 1.2 0.9	 0.0186 0.0139	22
Spalax leucodon [14]	310	0.77	0.0103	21
Rodentia: Bathyergidae [49] Cryptomys mechowi Cryptomys bocagei Cryptomys hottentotus amatus	 307 306.7 306.8	 0.60 0.74 0.63	 0.0094 0.0116 0.0098	 16 15 11

On one hand, we have shown, at least theoretically, that in mole-rats there exists a critical concentration of the high molecular weight of hyaluronic acid, such that guarantees the self-organization and fine regulation of the process [53], which guarantees tolerance to high levels of oxidative stress [54] and exhibits a high resistance to cancer [50,55].

On the a another hand, it is observed that the entropy production rate in the naked mole rat was suppressed approximately by 9% during hypoxia under a constant ambient temperature seems to reflect active suppression of metabolism. It is well known that mole-rats spend their entire lives underground in an extensive labyrinth of burrows which is sealed from the surface. These burrows provide them with a relatively safe, thermostable environment with high relative humidities, high CO2 O2 concentrations.

As can be seen, the breeding Ansell’s mole-rats (*Fukomys anselli*) exhibit greater complexity (> $\dot{S}_i$) than to the non-reproductive ones, which implies greater robustness [32,33,34]. The higher entropy production rate observed in reproductive females is not surprising *per se*, since reproduction is energy demanding, especially for lactating females and gives some stability and also robustness i.e. plasticity during the active period.

4. Conclusions and remarks

In summary, in this paper we have found:

1. The aging processes in rats, as in humans, appear as a kind of first order phase transitions, what we could call “biological phase transition”.

2. We have shown that the entropy production rate per body mass $\dot{S}_i$ as a function of the chronological age of the rats, behaves as a Lyapunov function and could be consider as a physical marker of biological age and a physical “pacemaker” for Lifespan.
3. The entropy production rate may provide new ways to monitor senescence and test the efficacy of specific interventions to modify the age-related decline in adaptive capacity.

More than answers there are still many questions to answer. We think that the present study forces us to design future standardized experiments of the metabolism on mole-rats, in relation to age, gender, environmental conditions (humidity, oxygen concentration, etc.) that can yield homogeneous data that allow a more reliable comparison between these and other rodents.

The current theoretical framework will hopefully provide a better understanding of the mechanism of senescence and contribute to improvements our knowledge in Lifespan and degenerative diseases.

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